Remarks/Arguments

Claims 1-72, as amended, are pending in the application for the Examiner's review and consideration. In a non-final Office Action, the Office rejected claims 1-72.

Claims 24, 25, 28, 35, 69, 70, and 71 have been amended to correct typographical errors and to present the claims in better form. No new matter has been added to the claims.

Claims 1-72 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. patent No. 6,506,767 ("'767 patent"), as well as its international counterpart PCT publication No. WO 99/01450 ("WO '450"). Applicants respectfully traverse. Because the specification of the '767 patent is identical to that of WO '450, Applicants will only address the '767 patent in this response.

The Federal Circuit in *In re Dembiczak*, 175 F.3d 994 (Fed. Cir. 1999), set forth three requirements to make out a *prima facie* case of obviousness under 35 U.S.C. § 103(a) in light of the prior art. In order to be *prima facie* obvious: (i) there must be some teaching or suggestion in the prior art to modify or combine references to form the claimed invention, (ii) there must be a reasonable expectation of success taught or suggested in the prior art, and (iii) all of the elements of the claimed invention must be found in the prior art. *See also* M.P.E.P. § 2143. In order to meet its burden to show that the claims are *prima facie* obvious in light of the prior art, the Office must expressly point to something in the references themselves, something in the nature of the problem to be solved, or something in the general knowledge of persons reasonably skilled in the art that would constitute objective evidence of a teaching or suggestion to combine the cited references. *See In re Lee*, 277 F.3d 1338 (Fed. Cir. 2002).

Preparation of Desloratadine Crystalline Form I

The '767 patent discloses the preparation of desloratadine crystalline Form I by crystallization from hexanol, methanol, dichloromethane, dioxane, or methyl isobutyl ketone. '767 patent, col. 4, ll. 18-37; col. 9, l. 62 to col. 11, l. 26 (examples 1-3).

Claims 1-9 recite processes for preparing desloratadine crystalline Form I comprising crystallization from acetonitrile, dimethylformamide, tetrahydrofuran, or diethylcarbonate. Claims 33-34 recite processes for preparing desloratadine Form I comprising precipitation from isobutyl acetate.

Claims 10-23 recite processes for preparing desloratadine Form I comprising precipitation from chloroform or ethyl acetate, wherein the precipitation is induced by addition of an anti-solvent. Claims 24-28 recite processes for preparing desloratadine Form I comprising precipitation from a C_1 to C_4 alcohol, wherein the precipitation is induced by addition of water.

As to claims 1-9 and 33-34, the '767 patent does not disclose or suggest the preparation of Form I from the solvents recited in the claims with any reasonable expectation of success. Polymorphism and polymorph generation are considered to be unpredictable by those skilled in the art. *See, e.g.,* Bernstein, J., POLYMORPHISM IN MOLECULAR CRYSTALS (Clarendon Press 2002); Byrn, S.R., SOLID-STATE CHEMISTRY OF DRUGS (Academic Press 1982); Brittian, H.G., POLYMORPHISM IN PHARMACEUTICAL SOLIDS (Marcel Dekker 1999). The disclosures of the '767 patent attest to this unpredictability. For example, the '767 patent discloses that crystallization from hexanol produces Form I, while crystallization from 3-methyl-1-butanol produces a mixture of Forms I and II. '767 patent, col. 4, ll. 22-26. Likewise, the '767 patent discloses that crystallization from methyl butyl ketone produces Form 1, while crystallization from its position isomer methyl isobutyl ketone produces a mixture of Forms I and II. Id. at col. 4, ll. 32-35. Thus, the disclosures of the '767 patent could at most provide the skilled artisan with an invitation to try to isolate Form 1 by crystallization from different solvents, but obvious to try is not the legal standard for obviousness under § 103. *See, e.g., In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988).

As to claims 10-28, the '767 patent does not disclose or suggest the preparation of Form I by precipitation from a solvent with the aid of an anti-solvent at all, let alone from the solvent/anti-solvent pairs recited in claims 10-28. Thus, the disclosures of the '767 patent would not motivate one of skill in the art to arrive at the processes recited in claims 10-28.

Preparation of Desloratadine Crystalline Form II

The '767 patent discloses the preparation of desloratadine crystalline Form II by crystallization from ethyl acetate or di-n-butyl ether. '767 patent, col. 11, ll. 28-46 (example 4); col. 11, l. 48 to col. 12, l. 8 (example 5).

Claim 29 recites a process for preparing desloratadine crystalline Form II comprising melting desloratadine to obtain a molten material, cooling the molten material to obtain a solid, and grinding the solid.

Claims 31-32 recite processes for preparing desloratadine crystalline Form II comprising precipitation from dimethyl carbonate. Claim 72 recites a process for preparing desloratadine crystalline Form II comprising crystallization from toluene.

As to claim 29, the '767 patent does not disclose the preparation of Form II by melting desloratadine in the absence of a solvent, followed by cooling and grinding, as recited in the claim. Further, the '767 patent does not suggest such a process. The only method for preparing Form II disclosed in the '767 patent is crystallization from a solvent. The '767 patent states "[o]nly ethyl acetate and di-n-butyl ether were found to produce crystalline polymorph form 2 substantially free of form 1." '767 patent, col. 4, ll. 38-40. The '767 patent does not disclose or suggest that solvent-free processes would be successful in producing Form II, and, thus, would not motivate one of skill in the art to arrive at the process recited in Claim 29.

As to claims 31-32 and 72, as discussed above, polymorph generation is unpredictable. Thus, the '767 patent's disclosure of crystallization from ethyl acetate or di-n-butyl ether would not teach or suggest the recovery of Form II from dimethyl carbonate or toluene to the skilled artisan with any reasonable expectation of success.

Preparation of a Mixture of Desloratadine Crystalline Forms I and II

The '767 patent discloses that mixtures of Forms I and II are produced when desloratadine is crystallized from 3-methyl-1-butanol, cyclohexanol, di-isopropyl ether, or methyl butyl ketone. '767 patent, col. 4, ll. 24-35.

Claim 30 recites a process for preparing a mixture of desloratadine crystalline Forms I and II comprising grinding desloratadine Form I.

Claims 38-40 recite processes for preparing a mixture of desloratadine crystalline Forms I and II comprising drying desloratadine Form I crystals obtained by crystallization from a C_1 to C_4 alcohol.

Claims 35-37, 55-56, 46-49, and 60-65 recite processes for preparing a mixture of desloratadine crystalline Forms I and II comprising precipitation or crystallization from isopropanol, isobutanol, iso-butyl acetate, a mixture of ethyl acetate or iso-butyl acetate with a C_1-C_4 alcohol, or a mixture of 2-propanol with toluene.

Claims 41-45, 50-54, 57-59, 66-67, and 68-71 recite process for preparing a mixture of desloratadine crystalline Forms I and II comprising precipitation from a solution, which is induced by the addition of an anti-solvent and/or by seeding. Claims 41-45 recite the use of an anti-solvent containing seeds of both Form I and Form II of desloratadine to precipitate the mixture. Claims 50-54 recite precipitation from iso-butyl acetate with the use of a C_5 to C_{12} aromatic hydrocarbon anti-solvent. Claims 57-59 recite precipitation from ethyl acetate by seeding with a mixture of Form I and Form II, as well as adding a C_5 to C_{12} aromatic hydrocarbon anti-solvent. Claims 66-67 recite precipitation from a mixture of 2-propanol and toluene with the use of a C_5 to C_{12} aromatic hydrocarbon anti-solvent. Claims 68-71 recite precipitation from a mixture of 2-propanol and toluene with the use of n-heptane as an anti-solvent.

As to claims 30 and 38-40, the '767 patent does not disclose the preparation of a mixture of Forms I and II by grinding crystals of Form I or drying crystals of Form I, as recited in the claims. Further, the '767 patent does not suggest these processes. The only method for preparing a mixture of Forms I and II disclosed in the '767 patent is crystallization from a solvent. The '767 patent does not disclose or suggest that solvent-free processes would be successful in producing a mixture of Forms I and II, and, thus, would not motivate one of skill in the art to arrive at the processes recited in claims 30 and 38-40.

As to claims 35-37, 55-56, 46-49, and 60-65, as discussed above, polymorph generation is unpredictable. Thus, the '767 patent's disclosure of crystallization from 3-methyl-1-butanol, cyclohexanol, di-isopropyl ether, or methyl butyl ketone would not teach or suggest the crystallization of a mixture of Forms I and II from the solvents recited in the claims to the skilled artisan with any reasonable expectation of success.

As to claims 41-45, 50-54, 57-59, 66-67, and 68-71, the '767 patent does not disclose or suggest the preparation of a mixture of Forms I and II by crystallization or precipitation from a solvent with the aid of an anti-solvent and/or seeding at all, let alone under the conditions recited in the claims. Thus, the disclosures of the '767 patent would not motivate one of skill in the art to arrive at the processes recited in the claims.

Therefore, based upon the above reasons, the rejection of claims 1-72 under 35 U.S.C. § 103(a) as obvious over the '767 patent and WO '450 cannot stand and should be withdrawn.

Conclusion

In view of the foregoing amendments and arguments, it is believed that the application is in condition for allowance, early notice of which would be appreciated. Should any outstanding issues remain, the Examiner is invented to telephone the undersigned at the telephone number indicated below to discuss them.

Respectfully submitted,

Dated: August 9, 2006 By: _____
Patrick J. Fay, Reg. No. 35,508